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The Patent Office
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NP10 8QQ

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Signed William Morell

Dated 13 April 2005

Patents Form 1/77

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — SMC 60647/GB/P1

2. Patent application number *(The Patent Office will fill in this part)* — 0406757.5 — 26 MAR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS

Patents ADP number *(if you know it)* — 07764137001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Process and Compounds

5. Name of your agent *(if you have one)* — GAIRNS, Raymond Stevenson

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Avecia Limited
Hexagon House
PO Box 42
Blackley
Manchester M9 8ZS

Patents ADP number *(if you know it)* — 69334720001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

0098980 26-Mar-04 10:45

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	Brief letter

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 26-3-04

Avecia Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

K.M.Pinder/G.Terry 0161 721 1361/2

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After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

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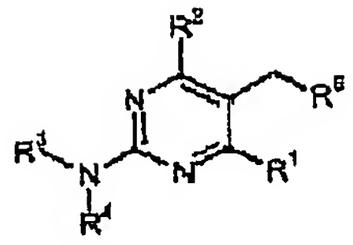
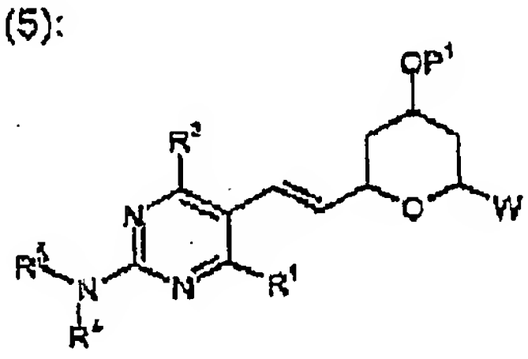


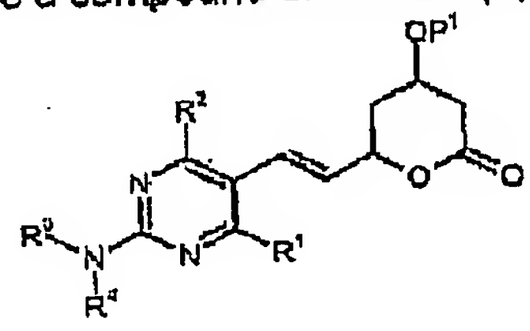
wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,

to give a compound of formula (5):



wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

d) when W represents $=OP^2$, removing any P^2 protecting group and oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, removal of any P^1 protecting groups, and optionally removing any additional protecting groups to give a compound of formula (7).

In step (e), any P^1 protecting groups and any additional protecting groups may be removed individually or together and prior to ring opening, during ring opening or after ring opening of the compounds of formula (5) or (6).

Protecting groups which may be represented by P^1 and P^2 include alcohol protecting groups, examples of which are well known in the art. Particular examples include tetrahydropyranyl, benzyl and methyl groups. Preferred protecting groups are silyl

groups, for example triaryl- and especially trialkylsilyl groups. Especially preferred examples are trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenyl groups.

Protecting groups which may be represented by P^1 and P^2 may be the same or different. When the protecting groups P^1 and P^2 are different, advantageously this may allow for the selective removal of only P^1 or P^2. Preferably, when the protecting groups P^1 and P^2 are different, P^1 is a silyl group and P^2 is a methyl group.

Protecting groups which may be represented by R^3 and R^4 include amine protecting groups, examples of which are well known in the art. Particular examples include benzyl groups, carbamates (such as CBZ, Boc, Fmoc), phosphate, thiophosphate, silyl groups and, when R^3 and R^4 together are a single protecting group, an imine group.

Hyrdoxylation of compounds of formula (1) can be achieved by methods known in the art for displacing a halo group with a hydroxide source. Preferably, the process comprises contacting the compound of formula (1) with a source of hydroxide. Hydroxide sources include hydroxide salts, especially ammonium or alkali metal hydroxides, particularly lithium, sodium or potassium hydroxide, and various aqueous media such as water in the presence of basic media such as N-methylpyrrolidinone, HMPA, Al_2O_3, $CaCO_3$, Na_2CO_3, K_2CO_3 or KO_2/18-crown-6, silver salts such as $AgNO_3$ or Ag_2O, or oxidants such perbehzioc acid. A particularly preferred process comprises contacting the compound of formula (1) with 5 molar equivalents of KOH in the presence of dimethylsulfoxide solvent at a temperature of, for example, about 50°C.

Alternatively, hydroxylation may be achieved by first displacing the halogen with a leaving group such as acetate, triflate or sulphate optionally in the presence of a silver salt, then displacing the leaving group with a hydroxide source. A particularly preferred process comprises contacting the compound of formula (1) with 3 molar equivalents of NaOAc in the presence of dimethylformamide solvent and tetra-n-butylammonium chloride at a temperature of, for example, about 100°C, isolating the acetyl compound and contacting with potassium carbonate in the presence of methanol solvent and at a temperature of, for example, about 0°C.

Oxidation of compounds of formula (2) can be achieved using oxidation systems known in the art for the oxidation of alcohols, especially those known in the art for the oxidation of primary alcohols. Examples include oxidation with Dess-Martin periodinane, bromine, Swern oxidation or various metal based oxidations such as Fetizon reagent, manganate based reagents, and chromate based reagents such as Collins reagent. Swern oxidation is preferred. When Swern oxidation is employed, preferred conditions comprise the use of dimethyl sulphoxide and oxalyl chloride or bromine in a solvent such as dichloromethane or dichlormethane/THF mixtres, at reduced temperature, such as from 0 to -100°C, preferably –50 to -80°C. Preferably, reagents are added at reduced temperature, such as –30 to -80°C, and then once all reagents are added, the reaction mixture is allowed to warm to 15 to 20°C.

The coupling of the compound of formula (3) with the compound of formula (4) may employ conditions analogous to those given in WO01/85702 for the corresponding coupling of a compound of formula (4). The conditions preferably comprise refluxing the compounds of formula (3) and (4) in a hydrocarbon solvent, such as toluene or cyclohexane, or mixtures thereof, followed by contact with aqueous acid, such as aqueous HCl.

Alkyl, aryl, alkoxy or aryloxy groups which may be represented by R^7 and R^8 include C_{1-6}alkyl groups, such as methyl and ethyl groups, C_{6-12}aryl groups, such phenyl, tolyl or naphthyl, C_{1-6}alkoy groups, such as ethoxy groups, and C_{6-12}aryloxy groups such as phenoxy groups.

Anions which may be represented by X include halide.

R^6 preferably is $P(=O)R^7R^8$ where R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group.

When W represents OP^2, the protecting group may be removed to form a hydroxy group by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

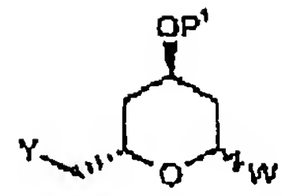
Oxidation of compounds formed by deprotection of compounds wherein W represents $-OP^2$ may employ conditions known in the art for the oxidation of pyranols to pyranones, and include those given in "Comprehensive Organic Transformations", R.C. Larock, 2nd Ed (1999) p 1670, published by Wiley VCH, incorporated herein by reference. Preferred oxidation systems include Ag_2CO_3/Celite, especially Celite J2, bromine or Swern.

Ring opening of the compounds of formula (5), when W represent =O or formula (6) may employ conditions known in the art for ring opening of a pyranone. Preferably, the ring is opened by contact with a base, such as sodium hydroxide. Conveniently, polar solvents are employed, for example methanol, acetonitrile, tetrahydrofuran or mixtures thereof.

Remaining protecting groups may be removed by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

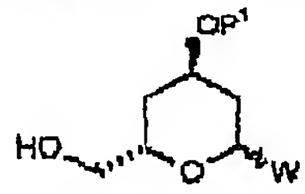
It will also be recognised that compounds of formulae (2), (3) and (5) may also be subjected to oxidation (when W represents –OH) or deprotection and oxidation (when W represents (-O-protecting group) to form the corresponding compound wherein W represents =O.

Preferred compounds of formula (1) are compounds of formula:



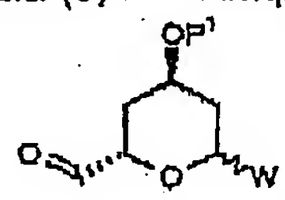
wherein W, P^1 and Y are as previously described.

Preferred compounds of formula (2) are compounds of formula:



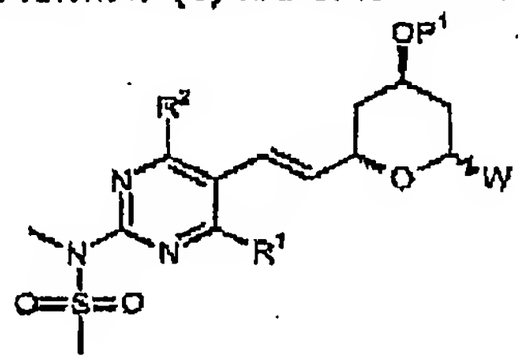
wherein W and P^1 are as previously described.

Preferred compounds of formula (3) are compounds of formula:



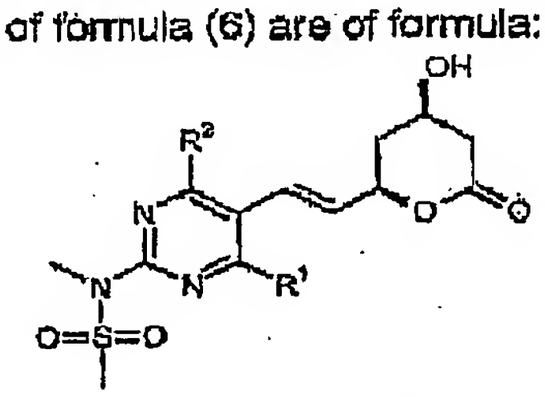
wherein W and P^1 are as previously described.

Preferred compounds of formula (5) are of formula:



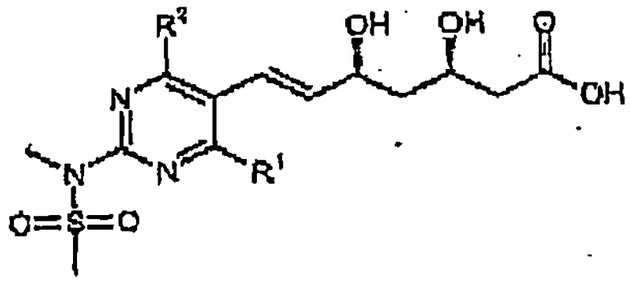
wherein R^1, R^2, W and P^1 are as previously described.

Preferred compounds of formula (6) are of formula:



wherein R^1 and R^2 are as previously described.

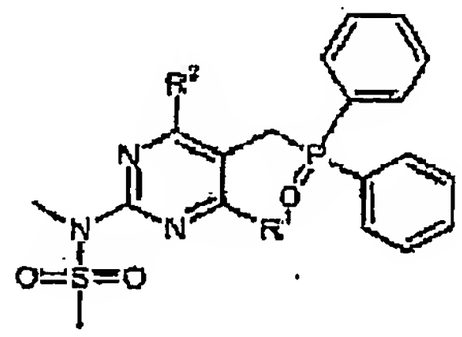
Preferred compounds of formula (7) are of formula:



wherein R^1 and R^2 are as previously described.

Compounds of formula (7) are advantageously converted to pharmaceutically acceptable salts, especially their calcium salts (for example WO01/60804) .

Compounds of formula (4) are advantageously prepared by the methods given in WO00/49014 and WO01/85702. Particularly preferred compounds of formula (4) are compounds of formula:

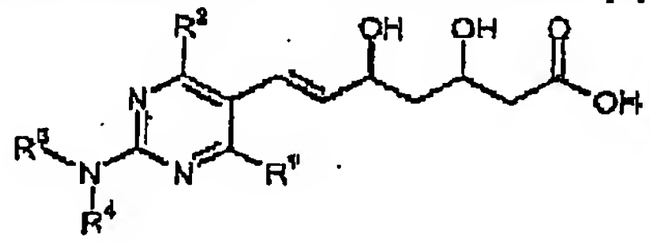


Compounds of formula (1) are advantageously prepared by enzyme catalysed condensation of acetaldehyde and 2-haloacetaldehyde, for example using the method given in US patent 5,795,749.

Compounds of formulae (2) and (3) and, when W is OP^3, formula (5) form further aspects of the present invention.

CLAIMS

1. a process for the preparation of a compound of formula (7):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

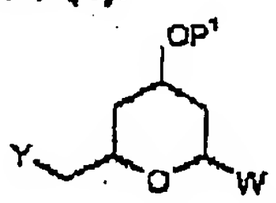
R^2 represents an aryl group, preferably a 4-fluorophenyl group;

R^3 represents hydrogen, a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and

R^4 represents hydrogen, a protecting group or a SO_2R^5 group where R^6 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

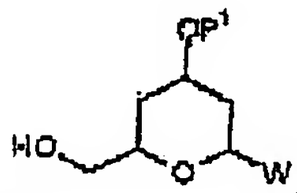
which comprises

a) hydroxylating a compound of formula (1):

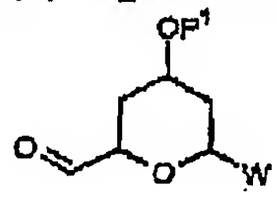


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

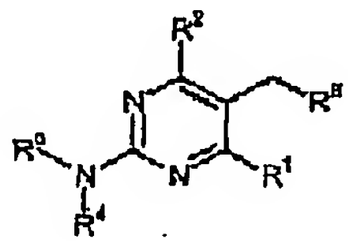
to give a compound of formula (2):



b) oxidising the compound of formula (2) to give a compound of formula (3):

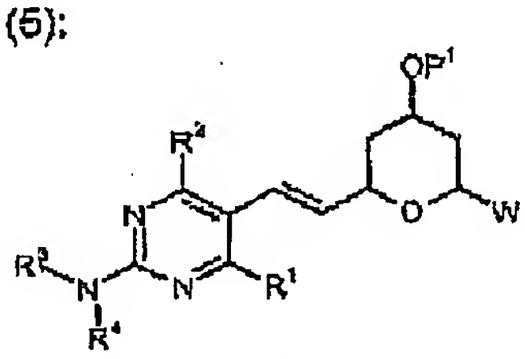


c) coupling the compound of formula (3) with a compound of formula (4):



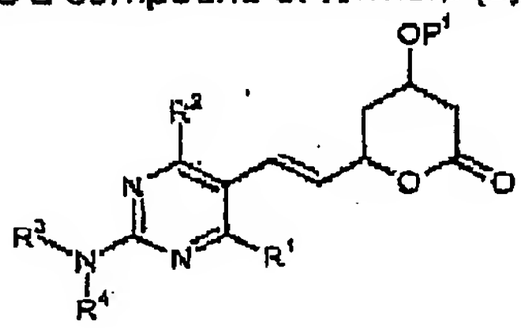
wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,

to give a compound of formula (5):



wherein R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group,

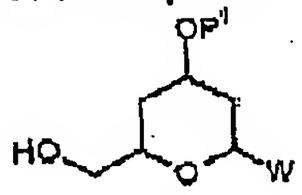
d) when W represents $-OP^2$, removing any P^2 protecting group and oxidising the compound of formula (5) to give a compound of formula (6):



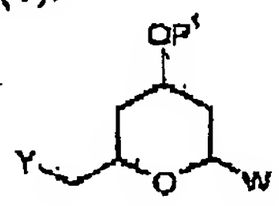
and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, removal of any P^1 protecting groups, and optionally removing any additional protecting groups to give a compound of formula (7).

2. A process for the preparation of a compound of formula (2):

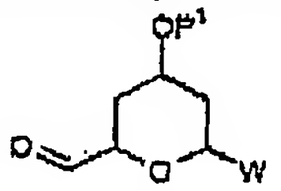


hydroxylating a compound of formula (1):

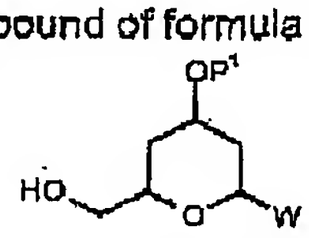


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

3. A process for the preparation of a compound of formula (3):

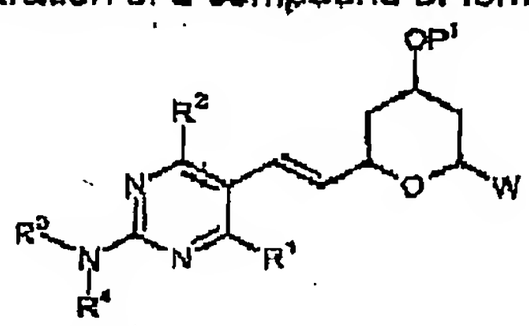


which comprises oxidation of a compound of formula (2):

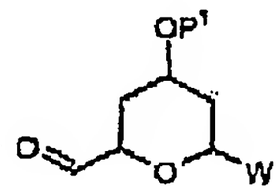


wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen a protecting group.

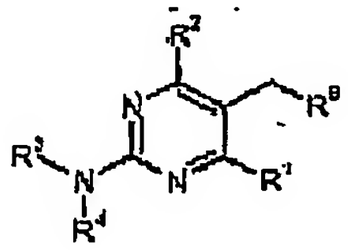
4. A process for the preparation of a compound of formula (5):



which comprises coupling the compound of formula (3):



with a compound of formula (4):



wherein

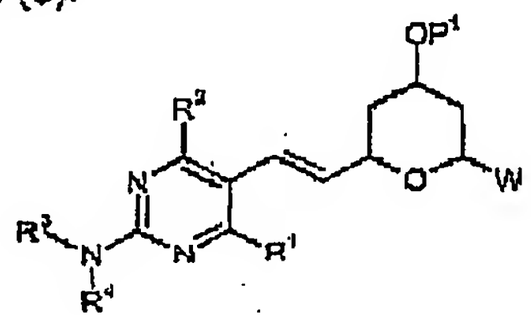
R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

R^2 represents an aryl group, preferably a 4-fluorophenyl group;

R^3 represents a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group;

R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group; and
R^6 represents $(PR^7R^8)^+X^-$ or $P(=O)R^7R^8$ in which X is an anion and R^7 and R^8 each independently is an alkyl, aryl, alkoxy or aryloxy group, preferably a phenyl group,
P^2 represents hydrogen or a protecting group; and
W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

6. A compound of formula (5):



wherein
R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;
R^2 represents an aryl group, preferably a 4-fluorophenyl group;
R^3 represents hydrogen, a protecting group or an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group;
R^4 represents a protecting group or a SO_2R^5 group where R^5 is an alkyl group, such as a C_{1-6} alkyl group, and preferably a methyl group;
P^1 represents hydrogen or a protecting group; and
W represents =O or $-OP^2$, in which P^2 represents hydrogen a protecting group.

PATENT COOPERATION TREATY

PCT/GB05/001099

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GAIRNS, Raymond, Stevenson
Avecia Pharmaceuticals limited
Intellectual Property Group
PO Box 42
Hexagon Tower
Blackley, Manchester M9 8ZS
ROYAUME-UNI

Date of mailing *(day/month/year)* 25 May 2005 (25.05.2005)	
Applicant's or agent's file reference SMC 60647/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB05/001099	International filing date *(day/month/year)* 23 March 2005 (23.03.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 26 March 2004 (26.03.2004)
Applicant AVECIA PHARMACEUTICALS LIMITED et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* **An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
26 March 2004 (26.03.2004)	0406757.5	GB	09 May 2005 (09.05.2005)

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